BlueCross BlueShield of Alabama

Name of Policy:
Bendeka™ and Treanda® (bendamustine hydrochloride)

Policy #:	669	Effective Date:	June 30, 2017
Category:	Pharmacology	Last Review Date:	May 2017

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Bendeka/Treanda (bendamustine hydrochloride) is a bifunctional mechlorethamine derivative alkylating drug indicated for the treatment of chronic lymphocytic leukemia and indolent B-cell non-Hodgkin lymphoma. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. . The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of bendamustine remains unknown.

Policy:

Bendeka/Treanda (bendamustine hydrochloride) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of any of the following indications:

1. **Chronic lymphocytic leukemia** (CLL) when used as a single agent or in combination with Rituxan; **or**
2. **Relapsed or refractory classical Hodgkin lymphoma** when used as a single agent; **or**
3. **Non-Hodgkin lymphoma** (NHL) (i.e., adult T-cell lymphoma, AIDS related B-cell lymphoma, diffuse-large B-cell lymphoma, follicular lymphoma, gastric MALT lymphoma, mantle cell lymphoma, mycosis fungoides/Sezary syndrome, nodal marginal zone lymphoma, non-gastric MALT lymphoma, peripheral T-cell lymphoma, primary cutaneous B-cell lymphoma, primary cutaneous CD30+ T-cell lymphoproliferative disorders , splenic marginal zone lymphoma); **or**
4. **Relapsed or refractory Multiple Myeloma**; **or**
5. **Waldenström's macroglobulinemia** when used a single agent or in combination with Rituxan

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Chronic lymphocytic leukemia (CLL):

According to the NCI, in 2017 an estimated 20,110 individuals will be diagnosed with CLL in the U.S., and nearly 4660 deaths will occur. The American Cancer Society indicates approximately one-third of all new cases of leukemia are CLL, mainly affecting older adults.

Chronic lymphocytic leukemia (CLL) is an indolent form of Non-Hodgkin lymphoma (NHL) marked by immunologically less mature lymphocytes and manifested by progressive accumulation of these cells in the blood, bone marrow, and lymphatic tissues. The lymphocytes are characterized by immunophenotype (CD5- and CD23-positive B cells). Additionally, B-cell

antigens CD19 and CD20 are also co-expressed on CLL lymphocytes. CLL may progress to a generally enlarged lymphatic system as well as complications resulting from pancytopenia. According to the NCI, treatment with "conventional doses of chemotherapy are not curative" for individuals with progressing CLL. Therefore, treatments to prolong disease-free survival for indolent and active disease continue to be studied.

The FDA evaluated the safety and efficacy of bendamustine HCL in an open-label, randomized, controlled multicenter trial comparing bendamustine HCL to chlorambucil as first-line treatment in individuals with CLL. The study randomly assigned 301 previously-untreated participants with Binet Stage B or C (Rai Stages I-IV) CLL to bendamustine HCL (n=153) or chlorambucil (n=148). The populations in both groups were balanced. The reported overall response rate (ORR) was significantly higher in the bendamustine HCL group (59%) compared to those treated with chlorambucil (26%) ($p<0.0001$) with 8% versus < 1% complete response (CR) rate. The median progression-free survival (PFS) was 18 months for bendamustine HCL compared to 6 months for chlorambucil.

The National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology list 2A off-label recommendations for the use of bendamustine HCL with or without rituximab in treatment of CLL without del (17p)/TP53 as first-line therapy or for treatment of relapsed or refractory disease. The recommendations are based on evidence with uniform consensus. The peer reviewed literature consists of case series and randomized controlled trials.

Hodgkin Lymphoma, Classical:
Hodgkin lymphoma is a type of malignancy which starts in the lymphocytes, a type of white blood cell that fights infection. Hodgkin lymphoma most commonly affects people between the ages of 15 and 40 and people older than age 55. In Hodgkin lymphoma, cells in the lymphatic system grow abnormally and may spread beyond the lymphatic system. As the disease progresses, it compromises the body's ability to fight infection. Many initial signs and symptoms may be similar to those of influenza, such as fever, fatigue and night sweats. Eventually, tumors develop. Hodgkin lymphoma is distinguished by the presence of abnormal Reed-Sternberg cells with majority of cases expressing CD15 and CD30 on immunohistochemistry testing of tissue. In developed countries, classical Hodgkin lymphoma accounts for approximately 95% of all Hodgkin disease.

The National Comprehensive Cancer Network® (NCCN) Drugs and Biologics Compendium ™ and the NCCN CPG for Hodgkin disease include a 2A recommendation for off-label use of bendamustine HCL for relapsed or refractory Hodgkin lymphoma (HL). Based on preliminary results from a phase II trial, bendamustine:

> Was well tolerated and highly active in heavily pre-treated patients (including those who have failed HDT/ASCR) with relapsed or refractory disease, resulting in a ORR of 56% among evaluable patients (34 out of 36 patients enrolled). The ORR by intent-to-treat analysis was 53% (33% CR and 19% PR). The median response duration was 5 months.

Non-Hodgkin Lymphoma (NHL):
In 2017 an estimated 72,240 new cases of NHL will be diagnosed and nearly 20,140 deaths estimated in the United States. NHL is a collection of more than a dozen different cancers of the lymphatic system, which generates the body's immune defenses. This system includes a network of channels akin to blood vessels through which lymphocytes--important white blood cells of the immune system--patrol the body for invading microbes. Along these lymphatic routes in the neck, armpits, abdomen, and groin are clusters of bean-shaped lymph nodes that house platoons of the infection-fighting lymphocytes. These cells also cluster in areas that serve as gateways to the body, including the mucous membranes lining the respiratory and digestive tracts, and the skin. Lymphocytes travel in the bloodstream, as well. The lymphatic system also includes such organs as the spleen, thymus and tonsils.

According to the NCI, NHL can be divided into two prognostic groups: the indolent lymphomas and the aggressive lymphomas. Indolent NHL types have a relatively good prognosis with a median survival as long as 10 years, but they usually are not curable in advanced clinical stages. Early stage (stage I and stage II) indolent NHL can be effectively treated with radiation therapy alone. Most of the indolent types are nodular (or follicular) in morphology. The aggressive type of NHL has a shorter natural history, but a significant number of these individuals can be cured with intensive combination chemotherapy regimens. In general, with modern treatment of individuals with NHL, overall survival at 5 years is over 60%, and more than 50% of individuals with aggressive disease can be cured. The vast majority of relapses occur in the first 2 years after therapy. The risk of late relapse is higher in individuals with a divergent histology of both indolent and aggressive disease.

Indolent NHL is usually responsive to radiation therapy and chemotherapy. However, a continuous rate of relapse is usually seen in advanced stages. Individuals can be re-treated with considerable success as long as the disease histology remains low grade. Individuals who present with or convert to aggressive forms of NHL may have sustained complete remissions with combination chemotherapy regimens or aggressive consolidation with marrow or stem cell support.

In October 2008 the FDA approved the expanded use of bendamustine HCL (TREANDA), and in December (2015) the FDA approved BENDEKA for the treatment of individuals with indolent B-cell NHL that progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.

Throughout the years, the methods to classify the various types of lymphomas have been modified as technology and understanding of the role of genetics and immunology have increased. The historical table of classifying NHL by the International Working Formulation (IWF) had been updated by the Revised European American Lymphoma (REAL) classification. Subsequently, the classification has been updated as a result of collaboration between the European and American hematology and pathology societies and the World Health Organization (WHO). For clinical utility, NHL can also be divided into indolent or aggressive lymphomas. The use of a particular classification is based on the practitioner's preference. A widely utilized tool as a prognostic indicator for NHL is the International Prognostic Indicator. The index was developed based on clinical characteristics to predict the outcome of aggressive NHL.

Individuals with indolent lymphoma may experience a relapse with a more aggressive histology. Documentation of conversion to a more aggressive histology requires an appropriate change to a therapy applicable to that histologic type. Histologic conversions or transformations are typically treated with the regimens prescribed for aggressive NHL.

Modified REAL Classification of Lymphoproliferative Diseases:

Non-Hodgkin
Indolent lymphoma/leukemia

A. Follicular lymphoma (follicular small cleaved cell [grade 1], follicular mixed small cleaved and large cell [grade 2], diffuse small cleaved cell)
B. Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
C. Lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia)
D. Extranodal marginal zone B-cell lymphoma (MALT lymphoma)
E. Nodal marginal zone B-cell lymphoma (monocytoid B-cell lymphoma)
F. Splenic marginal zone lymphoma (splenic lymphoma with villous lymphocytes)
G. Hairy cell leukemia
H. Mycosis fungoides/Sézary syndrome
I. T-cell granular lymphocytic leukemia
J. Primary cutaneous anaplastic large cell lymphoma/lymphomatoid papulosis (CD30+)
K. Nodular lymphocyte predominant Hodgkin lymphoma

Aggressive lymphoma/leukemia

A. Diffuse large cell lymphoma (includes diffuse mixed cell, diffuse large cell, immunoblastic, T-cell rich large B-cell lymphoma)
    1. Mediastinal large B-cell lymphoma
    2. Follicular large cell lymphoma (grade 3)
    3. Anaplastic large cell lymphoma (CD30+)
    4. Extranodal NK/T-cell lymphoma, nasal type/aggressive NK-cell leukemia/blastic NK-cell lymphoma
    5. Lymphomatoid granulomatosis (angiocentric pulmonary B-cell lymphoma)
    6. Angioimmunoblastic T-cell lymphoma
    7. Peripheral T-cell lymphoma, unspecified
        a. Subcutaneous panniculitis-like T-cell lymphoma
        b. Hepatosplenic T-cell lymphoma
    8. Enteropathy-type T-cell lymphoma
    9. Intravascular large B-cell lymphoma
B. Burkitt's lymphoma/Burkitt's cell leukemia/Burkitt's-like lymphoma
C. Precursor B- or T-cell lymphoblastic lymphoma/leukemia
D. Primary central nervous system (CNS) lymphoma
E. Adult T-cell leukemia/lymphoma (HTLV 1+)
F. Mantle cell lymphoma
G. Polymorphic post-transplantation lymphoproliferative disorder (PTLD)
H. AIDS-related lymphoma
I. True histiocytic lymphoma
J. Primary effusion lymphoma

K. B- or T-cell prolymphocytic leukemia
L. Plasmablastic lymphoma

The FDA expanded approval of bendamustine HCL was based on efficacy evaluated in a multicenter, open-label, single-arm trial of 100 participants with indolent B-cell NHL that had disease progression during or within 6 months of treatment with rituximab or a rituximab-containing regimen. Study findings reported by Kahl and colleagues found "an ORR of 75% (a 14% complete response rate, a 3% unconfirmed complete response rate, and a 58% partial response rate) was observed. The median DOR was 9.2 months, and median PFS was 9.3 months." Safety was evaluated in 176 participants, the above 100 participants with an additional 76 participants with B-cell NHL who received prior rituximab. According to the FDA news:

> The most frequently reported non-hematologic adverse reactions reported were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%) and pyrexia (34%). The most frequently reported abnormal hematologic laboratory values were lymphopenia (99%), leukopenia (94%), anemia (88%), neutropenia (86%), and thrombocytopenia (86%).
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> Grade 3 or 4 adverse reactions were reported in 71% of combined safety populations. The most frequently reported non-hematologic Grade 3 or 4 adverse reactions were fatigue (11%), febrile neutropenia (6%), and pneumonia, hypokalemia and dehydration (each reported in 5% of patients). The most frequently reported grade 3 or 4 hematologic laboratory abnormalities were lymphocytopenia (94%), neutropenia (60%), leukopenia (56%), thrombocytopenia (25%), and anemia (11%).

The NCCN Drugs and Biologics Compendium and the NCCN CPG for non-Hodgkin lymphoma lists off-label use of bendamustine HCL (with or without rituximab) for individuals with both indolent and aggressive forms of NHL. The recommendations were based on both level 1 and 2A category of evidence and uniform consensus. The panel reported that bendamustine HCL:

> Has shown promising results with acceptable toxicity in patients newly diagnosed as well as heavily pretreated relapsed or refractory indolent or mantle cell histologies or transformed NHL.

Multiple myeloma:
Multiple myeloma is a systemic malignancy of plasma cells that accumulate in the bone marrow, leading to destruction of bone and failure of the bone marrow. The American Cancer Society has estimated 30,280 new cases of multiple myeloma in the United States in 2017, with an estimated 12,590 deaths. The disease is staged by estimating the myeloma tumor cell mass on the basis of the amount of monoclonal (or myeloma) protein (M-protein) in the serum and/or urine along with various clinical parameters, such as the hemoglobin and serum calcium concentrations, the number of lytic bone lesions, and the presence or absence of renal failure. The stage of the disease at presentation is a strong predictor of survival, but has little influence on the choice of therapy since almost all individuals (except for those with solitary bone tumors or extramedullary plasmacytomas) have generalized disease. The age and general health of the individual, prior therapy and the presence of complications of the disease influence treatment selection. Clinical response is transitory in all cases despite achievement of complete remission

and apparent eradication of disease, and multiple myeloma is considered incurable with current approaches.

Bendamustine HCL is used in individuals previously treated for myeloma with relapsed disease and in progressive or refractory disease. The NCCN panel for their practice guideline for multiple myeloma evaluated use of bendamustine HCL for the treatment option of relapsed/refractory multiple myeloma, the NCCN panel offers a 2A recommendation based on committee consensus, data from two case series and the outcomes of a phase I/II trial. In individuals treated with bendamustine alone:

The ORR was 55%, with a median PFS of 26 weeks for all patients and 36 weeks for patients who received higher doses of bendamustine (90-100mg/m^2). Toxicity was mild and mainly hematologic. A retrospective analysis of 39 patients reported that bendamustine is effective and tolerable in patients with advanced progressive MM, with an ORR or 36%.

A multicenter phase I/II trial investigated the combination of bendamustine, lenalidomide, and dexamethasone as treatment for patients (n=29) with relapsed MM. PR rate was seen in 52% (n=13) of patients, with VGPR in 24% (n=6) of patients. The median PFS in the trial was 6.1 months (95% CI, 3.7-9.4 months), and the one-year PFS rate was 20% (95% CI, 6%-41%).

Waldenström's Macroglobulinemia
Waldenström's macroglobulinemia is an indolent lymphoproliferative disease also known as Lymphoplasmacytic lymphoma. Waldenström's macroglobulinemia usually includes involvement of the bone marrow, lymph nodes, spleen, and may develop into hyperviscosity syndrome. The monoclonal serum paraprotein immunoglobulin M (IgM) gammopathy is typically associated with Waldenström's. Treatment of acute symptoms usually includes plasmapheresis; long-term management of individuals with serum viscosity of four centipoise or less is typically managed with chemotherapeutic agents.

The NCCN CPG for Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma lists the off-label use of bendamustine HCL with or without rituximab as primary therapy, use in disease unresponsive to primary therapy or progressive or relapsed disease. These recommendations were based on a 2A category of evidence and uniform consensus. The peer-reviewed literature consists of case series and randomized, multicenter phase III trials.

Key Words:
Bendeka, Treanda, bendamustine hydrochloride, Hodgkin lymphoma, Non-Hodgkin lymphoma, multiple myeloma, Waldenström macroglobulinemia.

Approved by Governing Bodies:
On March 20, 2008, the U.S. Food and Drug Administration (FDA) approved bendamustine HCL (TREANDA), and on December 7, 2015 approved (BENDEKA), for use as a first-line therapy for individuals with CLL. Bendamustine HCL (BENDEKA) is a low-volume preparation with short infusion time, replacing TREANDA after March 31, 2016, at which time TREANDA

will be discontinued from the market. The FDA approved TREANDA and BENDEKA based on the same pivotal trials.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

J9033	Injection, bendamustine HCL (Treanda), 1mg
J9034	Injection, bendamustine HCL (Bendeka), 1mg

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Policy History:

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